Remarks

I. Status of the Application and Claims

The present application is a request for reissue of U.S. 6,479,551. As filed, the application had a total of 41 claims. Claims 1-4 and 30-33 were cancelled in a Preliminary Amendment included at the time of filing. No claims were added or cancelled herein and, therefore, the claims presently pending are 5-29 and 34-41.

II. Objections to the Specification

On pages 7 and 8 of the Office Action, the Examiner requires Applicants to cancel an amendment that they introduced to the specification in a Preliminary Amendment filed on March 29, 2004. This amendment related to a reference by Poyser, *et al.* As discussed previously, Applicants did not believe that the original paragraph contained any statements that were untrue, but felt that the amendment better reflected the teachings of the Poyser reference. Thus, Applicants have cancelled their previous amendment. If the Examiner believes that canceling the entire text referring to the Poyser reference would be preferable, then Applicants would be willing to do that as well.

III. The Amendments

Applicants have amended several claims in response to rejections made by the Examiner. In particular, claims 5 and 34 have been amended so that they now refer to specific types of acid-base storage stabilized dosage forms. These changes were made in response to the rejection of claims under 35 U.S.C. § 112 appearing on pages 8-10 of the Office Action. In addition, Applicants have amended claims 11, 20 and 39 so that acetaminophen is now referred to as an analgesic, rather than as an NSAID. In order to maintain consistency, other claims were amended accordingly. None of these amendments add new matter to the application, and their entry is therefore respectfully requested.

The Rejections

I. Rejection of Claims Under 35 U.S.C. § 112

On pages 8-10 of the Office Action, the Examiner rejects claims under 35 U.S.C. § 112. For the most part, the Examiner's arguments appear to be that claims to acid-base storage

stabilized dosage forms are not enabled in their full scope because Applicants do not teach every way that such dosage forms could be made. However, the Examiner suggests that such claims *are* enabled for dosage forms in which analgesic or metoclopramide are barrier coated or in separate layers of a multilayered dosage form (see page 8, last paragraph). Although Applicants do not agree with the Examiner's assessment, in the interest of furthering the prosecution of this case, claims to acid-base storage stabilized dosage forms have been limited to correspond to the particular types of dosage forms that the Examiner indicates are enabled.

The Office Action also suggests that it would require undue experimentation to determine formulations in which there was *both* a barrier coating and coordinated delivery. However, it appears that the Examiner is assuming that a single membrane would have to fulfill both functions, *i.e.*, it would be necessary to have a single membrane that both served as a barrier coating and also controlled the timing of drug release. However, it should be remembered that acid-base storage stabilization is concerned with dosage forms prior to the time that they are ingested by a patient. Thus, a coating may be used that separates metoclopramide from analgesic during storage and which immediately dissolves upon ingestion. There may also be a second coating which surrounds the analgesic in dosage forms and controls its rate of release, *e.g.*, based upon the type of polymer present in the coating and/or its thickness. Thus, it is possible to produce dosage forms that fulfill both the function of acid-base storage stabilization and coordinated delivery using standard methodology known in the art.[1]

The Examiner also rejects claims 11, 20 and 39 under 35 U.S.C. § 112, second paragraph, apparently because claims refer to acetaminophen as an NSAID, when it is not recognized as being an NSAID in the art. In order to overcome this rejection, Applicants have amended claims so that they now only refer to acetaminophen as an analgesic.

In light of the amendments made herein and the discussion above, Applicants believe that the Examiner's rejection of claims under 35 U.S.C. § 112 has been overcome. It is therefore respectfully requested that this rejection be withdrawn.

---

1 Certain of the references that have been cited by the Examiner describe methodology that can be used with respect to either barrier coating drugs or producing coatings that control drug release.

II. Rejection of Claims Under 35 U.S.C. § 103

On pages 10-17 of the Office Action, the Examiner rejects all pending claims under 35 U.S.C. § 103. Essentially three different rejections are made. The first is based upon the combination of Hsiao, *et al.* (U.S. 5,885,616) with Poyser, *et al.* (U.S. 4,325,971), Tfelt-Hansen, *et al.* (*Lancet 346*:923-926 (1995)), Pradalier, *et al.* (*Headache 28*:550-557 (1998)), Beubler, Mandell, Ferrari, *et al.* and Ross-Lee, *et al.* (*Eur. J. Clin. Pharmacol. 24*:777-785 (1983)). The Examiner alleges that Hsiao, *et al.* teaches a multilayer dosage form which may contain aspirin and metoclopramide. Poyser is cited as teaching combinations of analgesic, such as paracetamol and that metoclopramide potentiates the effects of analgesics. The reference by Tfelt-Hansen is alleged to teach that aspirin may be combined with metoclopramide to treat migraine headache and similarly, Ross-Lee is cited as teaching that pretreatment of patients with metoclopramide overcomes gastric stasis that accompanies migraine headache attacks. The remaining references, *i.e.*, Pradalier, Beubler and Mandell are cited as teaching that various NSAIDs are effective in treating migraine headache, and Ferrari is cited as teaching that vasoconstrictors can cause migraine headache rebound. These teachings are alleged to be sufficient in combination to make Applicants' claimed invention obvious.

In a second rejection, the Examiner uses the same group of references discussed above but replaces Hsiao with Newton, *et al.* (U.S. 4,938,967) in view of Raff (U.S. 3,279,998). Newton and Raff are cited as teaching tablets which contain an immediate release layer of drug, together with a sustained release layer. The other references are cited for the reasons described above. The Examiner argues that the references would have been combined to produce a dosage form in which metoclopramide and analgesic are in separate layers of a dosage form because of knowledge provided by the references that pretreatment of patients with metoclopramide increases the effectiveness of a subsequently administered NSAID in treating migraine headache.

Finally, the Examiner rejects claims based upon Shah, *et al.* (U.S. 6,126,969) in view of the references above. The Shah reference is cited as teaching dosage forms in which one of the drugs present is coated to provide sustained release. The other references are cited for the same reasons discussed above.

Applicants respectfully traverse this rejection.

It is Applicants' position that none of the references recognize a problem with degradation of drug potency during storage due to an interaction between metoclopramide and acidic NSAIDs. As a result, even though the prior art discloses the use of dosage forms in which drugs are separated from one another, there would be no incentive to use those dosage forms with metoclopramide and an acidic NSAID. Applicants also contend that none of the references disclose coordinated delivery as this term is defined in the pending application. Below, Applicants review each of the references that were cited and then briefly comment on the rejections as they apply to different claims.

A. Review of References Cited

Hsaio: The reference by Hsiao does disclose tablets or beads having multiple layers for delivering drugs. The reference also lists metoclopramide and acetaminophen, among many other drugs, as compounds that can be used in the disclosed dosage forms. However, it never suggests that metoclopramide and acetaminophen (or any other analgesic) should be used *together* in a single dosage form or that, during storage, they should be kept separate from one another in order to maintain potency. Hsiao also never suggests the type of coordinated delivery required by Applicants' claims. It certainly does not suggest that degradation might occur if an acidic analgesic and metoclopramide are allowed to contact one another.

Poyser: Poyser may suggest the use of analgesics and metoclopramide, but it fails to recognize the importance of separating acidic NSAIDs from metoclopramide in order to prevent degradation during storage. One analgesic suggested for use by Poyser is paracetamol, which the Examiner alleges is coated with gelatin. However, as discussed in a previous response filed by Applicants in a related case, it is really not clear whether the gelatin in the paracetamol preparation used by Poyser actually surrounds the acetaminophen or is simply mixed with the acetaminophen.[2] However, even if the paracetamol is coated in the manner alleged, it would not be relevant to the present claims because paracetamol is a *basic* compound and the problems with degradation identified by Applicants is limited to interactions involving acidic compounds, such

2 See response filed on March 29, 2005 in connection with 10/255,036 (pages 10-11).

as naproxen. Not only does Poyser fail to recognize the problem of potential drug degradation during storage, but the reference actually appears to suggest making tablets in which aspirin is in direct contact with metoclopramide, a combination that should lead to rapid deterioration during storage. Poyser makes no suggestions whatsoever with regard to coordinated delivery.

Pradalier: Applicants do not dispute the Examiner's assertion that this reference teaches that NSAIDs are effective at treating migraine.

Tfelt-Hansen: Applicants agree that this reference teaches that there is gastric stasis during a migraine headache attack and that a combination of aspirin and metoclopramide may be given as a treatment. It should be noted, however, that the reference says nothing at all about a loss of activity during storage. In fact, it appears that the aspirin may have been given as a separate tablet. The reference also says nothing about coordinated delivery as this term is used by Applicants. The timing of metoclopramide and aspirin administration is not discussed at all in Tfelt-Hansen and, as mentioned previously, it appears that the two drugs may simply have been administered to patients as separate tablets.

Ross-Lee: This reference discloses the administration of aspirin with either oral or injected metoclopramide. The drugs were given separately in all instances, and the reference does not teach anything with respect to a loss of potency due to drug interactions that occur during storage or with respect to the coordinated release of drugs from a single tablet. It is impossible to say whether the timing of separately given oral tablets would match that reported by Applicants (see col. 8, lines 50-61 for a definition of coordinated as used in the present application) since the Ross-Lee reference does not provide any information on the rate at which tablets dissolve. However, if it is assumed that the tablets release drug immediately after ingestion, then the timing would not be the same. In this regard, it should be noted that oral aspirin was given three minutes after metoclopramide in the Ross-Lee study (see page 778, col. 2, last paragraph) whereas Applicants' definition of coordinated delivery requires that a therapeutically effective amount of analgesic not be available for 5-60 minutes after ingestion (see col. A, lines 57-59).

Newton and Raff: These references disclose multilayer dosage forms and, at least in the Newton reference, seem to suggest that drugs in different layers may be released at different times. However, the references never suggest the combination of metoclopramide and an NSAID and say nothing about the coordinated release of drugs as this term is used by Applicants. The references also do not say anything that would suggest that analgesics and metoclopramide should be separately compartmentalized in dosage forms to prevent degradation during storage.

Shah: Applicants view the Shah reference as disclosing essentially the same thing as Hsiao. It teaches multilayer dosage forms that may be used to release drugs at different rates. In addition, it includes metoclopramide and various NSAIDs in a very extensive list of drugs that could be used in the dosage forms.[3] It never suggests that metoclopramide and an analgesic should be combined in a single dosage form, kept separated from one another to prevent degradation or be released in a "coordinated" manner.

B. Claims to Acid-Base Storage Stabilized Dosage Forms

The present inventors have discovered that dosage forms containing metoclopramide and acidic analgesics rapidly lose potency during storage unless these two drug components are separated from one another. For example, when naproxen sodium is allowed to interact with metoclopramide, there is a loss of tablet potency of about 5% in two weeks and about 20 to 25% after three weeks at ambient temperature (see Example 1 in the application). Thus, claims 5 and 34-41 are directed to dosage forms in which acidic NSAIDs are separated from one another during storage either by being segreated into separated layers or by being surrounded by a membrane that prevents the drugs from interacting.

Applicants have never disputed allegations that multilayered tablets were known in the prior art or that technology existed that would have allowed for the preparation of compositions in which metoclopramide and analgesic are separated. However, there existed no motivation to make dosage forms of this type because the adverse effect of allowing metoclopramide and

3 The list of drugs extends for more than a full column of the patent.

analgesic to come into contact with one another was not recognized.[4] As discussed above, none of the references that have been cited by the Examiner recognize the necessity of separating acidic NSAIDs and metoclopramide. One of the references, Poyser, actually appears to suggest using dosage forms containing aspirin, an acidic NSAID, and metoclopramide that have been simply mixed together.

The Examiner appears to argue that an alternative motivation for separating metoclopramide and acidic NSAIDs, *i.e.*, other than the prevention of degradation, may have been provided by prior art suggesting that the administration of metoclopramide prior to the administration of NSAID may be used to reduce gastric stasis and increase NSAID absorption (Ross-Lee). Thus, the Examiner seems to allege that, knowing this, one would put metoclopramide in an outer layer of a tablet that dissolves quickly and NSAID in an inner, slowly dissolving layer.

In response, Applicants respectfully submit that the Examiner may be reading more into the Ross-Lee reference than is actually there. This reference does indicate that the administration of metoclopramide prior to the administration of NSAID increases absorption, but it does *not* suggest that simultaneous administration of the drugs would not have been equally effective. Thus, an advantage in pre-releasing metoclopramide is not disclosed. Even assuming, for the sake of argument, that the reference does teach sequential release as an advantage (and Applicants do not think this is the case), this still would not suggest that metoclopramide and NSAID should be segregated from one another. For example, metoclopramide might be placed by itself in an outer layer of a multilayer tablet with an inner layer containing both metoclopramide and NSAID. Such an arrangement would appear to make sense because one would want to maintain gastric motility throughout the time that NSAID was being absorbed.

---

[4] Probably the simplest and least expensive way to make a dosage form is to simply mix two drugs together. The situation is analogous to the making of a new chemical compound. Very often, it would have been possible for a chemist in the prior art to make a compound if he had wanted to do so. Nevertheless, claims to the compound may still be patentable if it was not actually made in the prior art and no motivation for carrying out its synthesis existed.

In light of these considerations, Applicants respectfully submit that the references cited by the Examiner do not render claims to acid-base storage stabilized dosage forms, *i.e.*, claims 5 and 34-41, obvious.

C. Claims to Compositions or Methods Involving the Coordinated Delivery of NSAID

Claims 6-13, 22-29 and 35-41 all involve compositions for the "coordinated delivery" of NSAIDs. Claims 14-21 involve treatment methods which utilize these compositions. It should be appreciated that the term "coordinated delivery" has been given a very specific meaning in the application. It is defined in col. 8, lines 50-61 as requiring that: a) metoclopramide be in the GI tract of a patient in a therapeutically effective concentration within 1-30 minutes after ingestion; b) that analgesic become present in effective concentrations in 5-60 minutes after ingestion; and c) that an effective level of analgesic not be attained until metoclopramide is already present at an effective concentration. To fall within the scope of the present claims, a single dosage form must sequentially time the release of drugs to meet these requirements.

The timing of drug delivery using a coordinated dosage form will necessarily be different than having individual components administered individually separated by an interval. Specifically, coordinated delivery should produce an overlap in drug release with the quantity of dissolved analgesic increasing at the same time that the effects of metoclopramide on gastric motility are increasing. Even though release is sequential, there are no large temporal gaps during which one drug is acting and the second drug has not yet arrived. This is important because the effects of metoclopramide can vary substantially among individuals. For example, one reference studying the effects of the combination of metoclopramide and the drug tolfenamic acid states:

> In single oral doses of 10 mg and 20 mg, metoclopramide did not significantly increase the rate of gastric emptying and there was almost a tenfold interindividual variation in peak plasma concentration of metoclopramide, possibly due to differences in the degree of "first-pass" metabolism. After oral dosing, the bioavailability varied between 32 and 97%.[5]

---

5 *Cephalalgia 4*:253-263, pg. 261, first full paragraph (1984), citations omitted.

As discussed above, none of the references cited by the Examiner describes coordinated delivery of the type required in the present application. Ross-Lee discloses that pre-administration of metoclopramide promotes the absorption of subsequently delivered NSAID, but says nothing about the timing of delivery within a single unit dosage form. In fact, as mentioned previously, Applicants do not believe that the disclosure even teaches that pre-administration of metoclopramide is preferable to metoclopramide and NSAID being administered at exactly the same time. It should also be appreciated that coordinated delivery is different than a sustained release dosage form. It is concerned with the time at which drugs become available for absorption. The drugs themselves may or may not be formulated for sustained release.[6]

For the reasons discussed above, Applicants respectfully submit that claims in the application that include coordinate delivery as a component, *i.e.*, claims 6-29 and 35-41, meet the non-obviousness requirement of patentability.

Conclusion

In light of the amendments and discussion above, Applicants believe that all of the Examiner's rejections have been overcome. It is therefore respectfully requested that these rejections be withdrawn and that the claims presently pending in the application be allowed. Early notice to this effect is earnestly solicited.

---

[6] Sustained release dosage forms would not necessarily be as advantageous as the Office Action appears to suggest. Although some migraine headaches can last for very long periods of time (as long as a week), most are only experienced by a patient for a few hours and many of the NSAIDs used have very long durations of action.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (202) 419-7013.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By: Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicants

Date: December 29, 2005
1801 K St., NW, Suite 401L
Washington, DC 20006
(202)419-7013